DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103780/0

March 7, 2002

Serono, Incorporated
Attention: Pamela Williamson Joyce
Vice President, Regulatory Affairs U.S.
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

This letter hereby issues Department of Health and Human Services U.S. License No. 1574 to Serono, Incorporated, Rockland, Massachusetts, in accordance with the provisions of Section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. This license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the product Interferon beta-1a. Interferon beta-1a is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.

Under this authorization, you are approved to manufacture Interferon beta-1a drug substance at _____. Final formulated drug product will be manufactured, filled, labeled and packaged at _____. In accordance with approved labeling, your product will bear the proprietary name Rebif®, and will be marketed in 0.5 mL pre-filled, single-use syringes containing 44 mcg Interferon beta-1a and in a Starter Pack of syringes containing 22 mcg Interferon beta-1a.

The dating period for Interferon beta-1a shall be 24 months from the date of manufacture when stored at 2 - 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for drug substance shall be 30 months when stored at -70°C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.

You are not currently required to submit samples of future lots of Interferon beta-1a to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specification.

Any changes in the manufacturing, testing, packaging or labeling of Interferon beta-1a, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). Your request for waiver of the requirement for assessment of Interferon beta-1a in pediatric patients was granted on April 24, 2000.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct post-marketing studies as described in your letters of March 1, 2002, March 5, 2002, and March 6, 2002 as outlined below:

Chemistry, Manufacturing, and Controls

1. To validate the precision of the ELISA screening assay and evaluate the sensitivity of this ELISA assay for antibodies to all forms of interferon beta used in the clinical trials. The results of these additional validation studies will be submitted by June 2002.

2. To perform additional studies to validate the precision, sensitivity, and reproducibility of the neutralizing antibody assay. In addition, to evaluate the sensitivity of the neutralization assay for antibodies to all forms of interferon beta used in the clinical trials. The results of these additional validation studies will be submitted by June 2002.

3. To validate the specificity of the neutralization assay. The results will be submitted by September 2002.

Clinical

4. To conduct a study in 100 patients to evaluate the immunosuppressive effects of chronic Rebif® treatment. The finalized protocol will be submitted to CBER by January 2003. Patient enrollment will be completed by December 2003, data collection completed by March 2004, and the final report with SAS datasets and applicable revised draft labeling will be submitted to CBER by June 2004.

5. To conduct a pregnancy registry study to prospectively collect data on 266 pregnant women exposed to Rebif® that will allow for an assessment of the potential risk from treatment to the mother, fetus and/or live born infant. The final protocol will be submitted to CBER by September 2002, and the study initiated by December 2002. Patient accrual will be completed by December 2007 and data collection completed by September 2008. The final study report, SAS datasets, and applicable revised draft labeling will be submitted to CBER by December 2008.

6. To conduct a randomized, double-blind, dose-comparison, parallel group study of 22 mcg and 44 mcg TIW subcutaneous doses of Rebif® in 750 patients with relapsing-remitting multiple sclerosis. The final protocol will be submitted to CBER by December 2002, and the study initiated by May 2003. Patient enrollment will be completed by October 2004, and the final patient will complete the study by October 2006. Data collection will be finalized by December 2006, and the final report, SAS datasets, and applicable revised draft labeling will be submitted to CBER by April 2007.

Protocols should be submitted to your IND — with a cross-reference letter to the BLA.

7. To submit a final study report, datasets and modified labeling based on 48-week results from study — by June 2002.

We acknowledge your agreement to incorporate appropriate assessments of depression, MRI effects and neutralizing antibodies in future moderate or large sized clinical studies.

It is required that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit three draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

Steven A. Masiello
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research

for Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research